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EXAMINER	
NOGUEROLA, ALEXANDER STEPHAN	

ART UNIT	PAPER NUMBER
1753	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,750	LIU ET AL.	
	Examiner	Art Unit	
	ALEX NOGUEROLA	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-14* is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/07/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *IDS of 12/10/2003*.

DETAILED ACTION

Claim Objections

1. Claims 15 and 19 are objected to because of the following informalities: in line 3 of claim 15 and claim 19 the first occurrence of "of the" should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 15-18 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Gao et al. ("High-Throughput detecting of Unknown Mutations by Using Multiplexed Capillary Electrophoresis with Poly(vinylpyrrolidone) Solution), *Anal. Chem.* 2000, *72*, 2499-2506) ("Gao").

Addressing claim 15, Gao discloses a method for determining the genotype of a first variant site of a first sample polynucleotide (abstract), comprising

providing amplicons of the first sample polynucleotide, the amplicons including the first variant site (abstract and Figure 3 – mutant homoduplex);

subjecting a first portion of the amplicons to denaturing and annealing to prepare a first mixture (Figure 3 and page 2501, first column, DNA Samples);

providing a first polynucleotide control, the first polynucleotide control comprising at least one polynucleotide strand able to form a duplex with a polynucleotide strand of at least one of the amplicons, the first polynucleotide control having a base corresponding to the first variant site of the sample polynucleotide, the identity of the base being known (Table 1; Figure 3; and page 2501, first column, DNA Samples);

combining a second portion of the amplicons with the first polynucleotide control to prepare a second mixture (page 2501, first column, DNA Samples);

subjecting the second mixture to denaturing and annealing to prepare a third mixture (page 2501, first column, DNA Samples);

subjecting the first mixture to temperature gradient electrophoresis (TGE) to obtain first electrophoresis data (note homoduplex electrophetograms in Figure 5);

subjecting the second mixture to temperature gradient electrophoresis (TGE) to obtain second electrophoresis data (note heteroduplex electropherograms in Figure 5); and

wherein the first and second electrophoresis data are indicative of the genotype of the first variant site of the first sample polynucleotide (first column on page 2503 –

"The mutation can be identified by the difference in electrophoretic patterns between homoduplex and heteroduplex").

Addressing claim 16, for the additional limitation of this claim see the first column on page 2503 and the first paragraph of the Conclusions on page 2506.

Addressing claims 17 and 18, for the additional limitations of these claims see DNA Samples on page 2501 and the first paragraph of Resolution Characteristics on page 2504.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. ("High-Throughput detecting of Unknown Mutations by Using Multiplexed Capillary Electrophoresis with Poly(vinylpyrrolidone) Solution), *Anal. Chem.* 2000, 72, 2499-2506) ("Gao").

Addressing claim 19, Gao discloses a method for determining the genotype of a first variant site of a first sample polynucleotide (abstract), comprising

providing amplicons of the first sample polynucleotide, the amplicons including the first variant site (abstract and Figure 3 – mutant homoduplex);

subjecting a first portion of the amplicons to denaturing and annealing to prepare a first mixture (Figure 3 and page 2501, first column, DNA Samples);

providing a first polynucleotide control, the first polynucleotide control comprising at least one polynucleotide strand able to form a duplex with a polynucleotide strand of at least one of the amplicons, the first polynucleotide control having a base corresponding to the first variant site of the sample polynucleotide, the identity of the base being known (Table 1; Figure 3; and page 2501, first column, DNA Samples);

combining a second portion of the amplicons with the first polynucleotide control to prepare a second mixture (page 2501, first column, DNA Samples);

subjecting the second mixture to denaturing and annealing to prepare a third mixture (page 2501, first column, DNA Samples);

subjecting the first mixture to temperature gradient electrophoresis (TGE) to obtain first electrophoresis data (note homoduplex electrophetograms in Figure 5);

subjecting the second mixture to temperature gradient electrophoresis (TGE) to obtain second electrophoresis data (note heteroduplex electropherograms in Figure 5); and

wherein the first and second electrophoresis data are indicative of the genotype of the first variant site of the first sample polynucleotide (first column on page 2503 – "The mutation can be identified by the difference in electrophoretic patterns between homoduplex and heteroduplex").

Gao does not mention providing second amplicons of the first sample polynucleotide, the second amplicons including the second variant site. Thus, Gao also does not disclose the steps in claim 19 that follow this providing step. However, barring evidence to the contrary, such as unexpected results, claim 19 essentially just repeating what is done by claim 15, which Gao teaches (as described above). Gao has shown that the genotype of a variant site of a sample polynucleotide can be identified by comparing electrophoresis data from TGE of the homoduplex with electrophoresis data form TGE of the heteroduplex prepared by subjecting and combining as claimed. On with ordinary skill in the art at the time of the invention would recognize that the method of Gao could also be applied to additional variant sites in the sample polynucleotide.

Addressing claims 20-22, similarly to claim 19, claims 21-23 essentially just repeat the additional steps of claims 16-18, which Gao teaches. See the first column on

page 2503; the first paragraph of the Conclusions on page 2506; DNA Samples on page 2501; and the first paragraph of Resolution Characteristics on page 2504

Addressing claims 23-26, barring a contrary showing, the additional limitations of these claims just repeat the limitations of claims 15-18, respectively, for a different sample polynucleotide, which Gao discloses. See Table 1 on page 2500 and Figure 5.

Allowable Subject Matter

8. Claims 1-14 are allowed.

9. The following is a statement of reasons for the indication of allowable subject matter:

a) Claim 1: the combination of limitations requires the steps of "combining the first amplicons with first and second different polynucleotide controls, the first and second polynucleotide controls differing by at least one base therealong, the position of the at least one differing base corresponding to the first variant site of the sample polynucleotide" and "deterring the genotype of the first variant site of the sample

polynucleotide based on the first and second electrophoresis data [for the first and second duplexes]." Claim 11: the combination of limitations requires the steps of "providing first and second polynucleotide controls, the first and second polynucleotide controls differing by at least one base therealong, the position of the differing base corresponding to a position of a variant site of the sample polynucleotide" and "determining the genotype of the sample polynucleotide based on the first and second electrophoresis data [for the first and second mixtures]."

Applicants, for example, subject the sample polynucleotide to TGE in the presence of one of the controls along a first separation lane, while along a second separation lane, or along the first separation lane at a preferably different time, the sample polynucleotide is subjected to TGE in the presence of a different control. The resulting electrophoresis data for separation with the two controls is than evaluated to determine first and second scores for the sample polynucleotide to produce a final call of the genotype for the sample. See in the specification page 12, line 7 to page 13, line 5.

The single control used by Gao et al. ("High-Throughput detecting of Unknown Mutations by Using Multiplexed Capillary Electrophoresis with Poly(vinylpyrrolidone) Solution), *Anal. Chem.* 2000, 72, 2499-2506) can be construed as two controls because (a) Applicant discloses that the first control and the second control can be the same (specification, page 12, lines 26-29) and Gao et al. discloses using the same control with the same polynucleotide sample under different conditions (Figure 6), and, alternatively, because (b) each strand of the control may be considered as a control, as

each strand of the control (which are inherently different from each there as they are complementary) combines with a strand of the sample polynucleotide. However, in the first case the two controls will not be different as claimed since they are the same. Additionally, Gao et al. does not determine the genotype of the first variant site of the sample polynucleotide based on the first and second electrophoresis data resulting from using the two controls that are the same. For example, in the situation where the first control is the same as the second control (in Figure 6 of Gao et al., as noted above) Gao et al. only observes that better resolution is obtained under one set of temperature conditions than another (page 2504, second column, first paragraph of Resolution Characteristics). The electrophoresis data under the two different conditions are not evaluated together as claimed. In the second case, even the first control and second control are construed as the two strands of the control in Gao et al. there is also no determining the genotype of the first variant site of the sample polynucleotide based on the resulting first and second electrophoresis data. The first and second electrophoresis data in this situation are the respective peaks for the annealing of the control strands with a strand from the sample polynucleotide (Figure 3). Gao et al. does not identify the peaks in the electropherograms of the heteroduplexes. Gao et al. instead looks for a pattern change between the electropherogram for the control(s) (heteroduplex) from the electropherogram for pure sample. The pattern change does not even require first and second peaks from the controls in the electropherogram of the heteroduplex , but may be the presence of peak shoulders or even broader peak width in the electropherogram for eh heteroduplx compared to the electropeherogram for the

sample polynucleotide (Figure 5 and page 2504, first sentence of the second paragraph of Resolution Characteristics).

b) Claims 2-10 depend directly or indirectly from allowable claim 1.

c) Claims 12-14 depend directly or indirectly from allowable claim 11.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alex Noguerola
Primary Examiner
AU 1753
September 26, 2006